Editorial

High Dose Immunotherapy with Stem Cell Rescue in Severe Systemic Sclerosis: An Idea That Is Moving Forward

Systemic sclerosis (SSc) is a multisystem autoimmune mediated disease whose mortality is very high, at least in the 10% to 15% of patients with the most severe form of disease. In that group of patients, predicted by the presence of early and rapid involvement of the skin plus early visceral involvement, the 5-year mortality is 50% or greater[1-4].

Although there are no clear therapeutic options for these individuals, several approaches are being examined. One such approach has been very early exploratory work with nonmyeloablative regimens and allogeneic transplantation, the most advanced research in this area is that related to high dose immunosuppressive therapy (HDIT) with autologous stem cell transplant (SCT). We and others have observed that HDIT coupled with autologous SCT provides many of these subjects with sustained and significant disease response.

We review the rationale for treating SSc patients with HDIT, discuss our experience with HDIT in subjects with SSc, examine the risks associated with HDIT, and describe a phase 3 study of HDIT with autologous stem cell transplant that is beginning in the United States.

Rationale for treating SSc patients with immunosuppressive therapy

There is abundant evidence that the immune system is intimately involved in the pathogenesis of the disease in the early stages of cutaneous SSc (Figure 1). Activated mononuclear cells are present in the dermis, particularly around blood vessels[5]. Antibody-dependent cellular cytotoxicity against fibroblasts and endothelium has been documented, as has the presence of early-activated endothelium that elaborates intracellular adhesion molecules to promote immunological cell chemotaxis. Further, activated T cells have been found in the lungs of patients with SSc, and immunologically activated fibroblasts are characteristic of SSc[3,6].

Experience treating SSc — efficacy

Based on the above, immunosuppressive therapy of SSc has been utilized to treat the disease. Plasma exchange has potentially shown some benefits. Antithymocyte globulin (ATG) has been effective in a case report, and cyclosporin A was reported to be effective in a subset of patients[7-13]. A recent 100 patient, open, nonrandomized trial of oral cyclophosphamide (CYC, 100 mg mean daily dose) appeared very encouraging for the alveolitis of SSc[14]. Finally, 2 controlled studies of methotrexate indicated that this drug was effective to treat some patients with systemic sclerosis[15].

Somewhat increased immunosuppressive therapy using intravenous CYC in doses between 750 and 1000 mg/m^2 monthly showed encouraging results. Fifteen of 31 patients showed encouraging and significant responses, in 13 pulmonary function stabilized, while in 2 patients pulmonary function declined[16,17].

General approaches to stem cell transplant

One might consider autologous SCT after HDIT, allogeneic transplant after HDIT, or nonmyeloablative SCT. Autologous SCT is effective for many neoplasms and lymphoproliferative diseases and is probably the safest of these. Preclinical studies and clinical experience suggest that remissions may be higher and more sustained after an allogeneic SCT, but the risks of graft-versus-host disease and mortality are higher. The rationale for nonmyeloablative allogeneic SCT is based on a supposition that mixed chimerism can suppress autoimmune disease. Although there is a case report in this issue showing possible success with such a nonmyeloablative regimen[18], its usefulness needs to be tested in a systematic way. Very limited experience indicates that there may be potential benefit from both nonmyeloablative and myeloablative, allogeneic SCT, but the risk of graft-versus-host disease is comparable after either of these regimens[18,19].

See Nonmyeloablative stem cell transplant in a patient with advanced SSc and SLE, *page 2513*

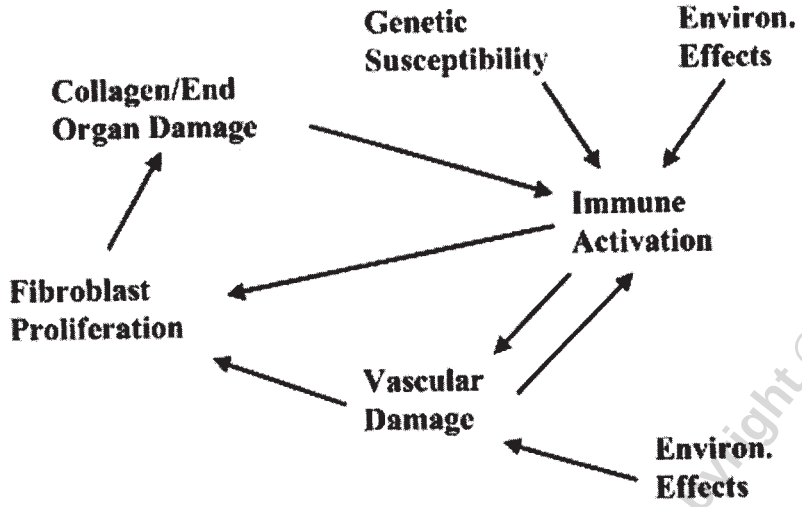

Figure 1. Pathogenesis of systemic sclerosis.

However, the approach with the most experience remains HDIT with autologous SCT, which will be reviewed here.

Autologous SCT after HDIT without total body irradiation (for the most part)

Significantly more immunosuppressive regimens have been used in patients with the most severe SSc. The European Group for Bone Marrow Transplantation (EBMT) registry documented a number of regimens using HDIT, usually with stem cell rescue, including: granulocyte-colony stimulating factor (G-CSF) with or without CYC (2–4 g/m^2) for mobilization; conditioning with CYC (120–200 mg/kg) or ATG, with or without total body irradiation (TBI); CYC plus other immunosuppressive drugs; BEAM regimen plus ATG; stem cell rescue with or without CD34+ (pluripotential) selection. In this very heterogeneous group of treatments, a positive benefit on skin disease was found in 69%, disease stabilized or improved in 81%, disease progression occurred in 19%, and survival was 73% at one year[20].

A French study of 12 patients treated in a single protocol employed CYC plus G-CSF for mobilization and 200 mg/kg CYC plus antilymphocyte globulin for conditioning (no TBI) and CD34 selected cells for "rescue." At 18 months, 8 of 11 subjects showed disease response at some time, with 5 of 8 relapsing within one year, and 36% died (one from treatment related toxicity and 3 from disease progression)[21].

High dose immunotherapy with total body irradiation

Combining HDIT with TBI further increases immunosuppression engendered by the immunosuppressive regimen. Because it is considered to be highly immunosuppressive, TBI is commonly used at a dose of 1200 cGy or more in combination with high dose CYC as a conditioning regimen before allogeneic hematopoietic SCT[22]. TBI has a homogeneous and predictable body distribution and has the potential for killing noncycling stem cells. Also, memory T cells are radiation-sensitive but seem to be resistant to CYC[20-23]. These properties of TBI make this immunosuppressive regimen more likely to be effective.

A pilot study of HDIT with TBI conducted in 19 patients with SSc in the United States was published in *Blood*[4]. Since publication, an additional 14 patients have been accrued in the pilot study. At 3 years, the median improvement in skin score was 77%, and the median change in the Health Assessment Questionnaire Disability Index (HAQ-DI) was 73% (starting HAQ-DI: 1.8). This degree of improvement in the skin score and HAQ-DI translates into major improvements in patients' quality of life and function. Overall survival to 3 years, using a Kaplan-Meier analysis, was 79%. After instituting lung shielding, transplant-related mortality was 12%, while 12% of the patients died from progressive SSc.

Another example of HDIT with TBI regimen for autoimmune disease is in multiple sclerosis (MS). A TBI-based regimen has been successfully used in 26 patients with MS, where clinically significant improvement or disease stabilization was documented in 73% of patients[24].

There are, therefore, some reasonable and encouraging pilot data regarding the efficacy of TBI in HDIT regimens for SSc and MS.

Comparing high dose immunotherapy regimens with or without TBI

In animal studies of adjuvant arthritis, TBI in combination with CYC was clearly more effective than high dose CYC alone[21]. In rats in which CYC alone was used at various doses, the arthritis score improved by 55%, while it improved by 91% in the rats treated with CYC plus TBI[21].

In humans, comparing the French study (which did not use TBI) and the US data, the results of HDIT with TBI were generally favorable. Numbers are far too small for statistical analysis, but efficacy and response duration using HDIT with TBI appeared about equal or somewhat better than without, while toxicity was not higher. A recent analysis of the registry data from the combined EBMT and the European League Against Rheumatism Autoimmune Disease Working Party suggested that for some autoimmune diseases (e.g., rheumatoid arthritis, RA), remission was less well sustained than for other diseases (e.g., SSc). Overall, the intensity of the immunosuppressive regimen used in RA was less than for other autoimmune disease subgroups, suggesting the possibility that higher degrees of immunosuppression may lead to better results and supporting the concept that TBI may be a valid approach for testing (personal communication, R. Saccardi).

Toxicity

The concept that higher degrees of immunosuppression may be more effective in SSc than less immunosuppression leads to the possibility that including TBI in the HDIT regimen may be an appropriate approach. However, the use of TBI in autoimmune diseases, and particularly in a disease associated with fibrosis such as SSc, raises some safety concerns[21,25]. In allogeneic protocols using CYC/ATG/TBI, acute toxicities may include early mortality, while longer-term toxicities may include primary ovarian failure, hypothyroidism, cataract, secondary malignancies, and the potential for increased pulmonary fibrosis.

Acute toxicities

Early experience with 800 cGy of TBI in SSc was associated with an unacceptably high acute pulmonary toxicity and mortality; after the first 8 patients the regimen was changed to include lung shielding to 200 cGy[4]. In the next 25 patients with SSc and in all 26 patients with MS (a total of 51 patients), no further acute pulmonary toxicities have occurred. There was a 10% decrement in the diffusing capacity (DLCO) and forced vital capacity (FVC) in the first 3 months after HDIT with TBI, a phenomenon common to all high dose chemoradiotherapies and not specific for SSc. By one year, however, these had recovered to baseline and by 3 years the median FVC had improved by 7% over baseline, while the DLCO improved by 3.5% (both stable with respect to baseline).

Longterm toxicities

Information on longterm toxicities after TBI has been collected in patients with hematologic and other malignancies (after both allogeneic and autologous hematopoietic SCT). No significant longterm toxicity data after HDIT currently exist for patients with autoimmune diseases.

Primary ovarian failure occurs with myeloablative TBI-based conditioning regimens required for allogeneic hematopoietic SCT with an incidence > 90%[26-28]. For patients > 26 years of age the risk of primary ovarian failure[26,27] will be about 60% to 70% after 200 mg/kg CYC as a single agent[27,28]. Primary ovarian failure is an inherent risk of any HDIT regimen with or without TBI. All patients will require pretreatment counseling on fertility and hormone replacement therapy.

The expected incidence of hypothyroidism and cataracts is 10% to 15% after HDIT with a TBI dose of 800 cGy[26,29]. Among 51 patients in the pilot studies of SSc and MS, 3 patients have developed hypothyroidism, one of which had an isolated increase in thyroid stimulating hormone.

No patient in the published studies of HDIT with TBI has thus far been observed to have developed cataracts.

The risk of secondary malignancies in patients given TBI at the revised doses used in the pilot studies of SSc and MS is not expected to be higher than with a chemotherapy-only regimen (e.g., CYC alone or busulfan plus CYC)[30]. In a multivariate analysis of risk factors for new solid cancers among 19,229 patients surviving at least one year after transplant, there was no increased risk of second cancers when < 1000 cGy of TBI was used. After single-fraction TBI, the relative risk was 0.9 (95% confidence interval 0.2–4.4), while after multiple-fraction TBI the relative risk was 1.2 (95% CI 0.3–5.7). From the EBMT Registry, a multivariate analysis of newly invasive solid cancers among 1036 patients surviving at least 5 years after transplant revealed the incidence of solid tumors was 5.1% after chemotherapy alone and 5.5% after chemotherapy plus TBI (not statistically different)[31]. In a University of Minnesota followup of up to 20 years among 3372 transplant patients, the relative risk of new malignancies was not higher among patients treated with chemotherapy plus TBI/total lymphoid irradiation than among patients treated with chemotherapy alone ($p = 0.27$)[32].

Another malignancy-associated risk that must be considered is increased myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML). Most published data regarding risks of MDS/AML after high dose chemoradiation therapy and autologous hematopoietic SCT arise from studies with patients diagnosed with non-Hodgkin's lymphoma or Hodgkin's disease. These patients have been heavily treated with alkylating agents prior to transplant. In the study from the Dana-Farber Cancer Institute and studies from other centers, pretransplant cytotoxic therapy was implicated as a significant contributor to the risk of MDS/AML after high dose chemoradiotherapy and autologous hematopoietic SCT. The incidence of MDS/AML after high dose chemoradiotherapy and autologous hematopoietic SCT has been reported to be comparable to some studies on longterm alkylating therapy. In the study from Dana-Farber Cancer Institute, 9 of the 20 MDS/AML patients were diagnosed within the first 2 years and 16 of the 20 were diagnosed

within the first 4 years of transplant[33]. In another study, by Krishnan, *et al* from the City of Hope National Medical Center, morphological evidence of MDS/AML developed a median of 1.9 years after autologous hematopoietic SCT, and there was no difference between the risks associated with chemotherapy alone versus those associated with chemotherapy plus TBI[34]. In the study by the Seattle consortium (using HDIT with TBI for SSc and MS), 2 cases of MDS were diagnosed among 51 patients followed for 2 or more years. As in second solid tumors then, HDIT, which includes alkylating agents, must be considered to have a potential risk of MDS/AML, but this does not seem to be increased when TBI is added to the regimen.

Finally, the potential risk of using TBI in SSc, a disease that has a predilection for fibrosis, needs to be considered, particularly in the lungs. As noted above, acute pulmonary toxicities associated with mortality have not occurred since institution of shielding the lungs to 200 cGy. On the other hand, there is a decrement in the DLCO in the first 3 months after HDIT with TBI. This decrement has essentially disappeared by the end of one year, with pulmonary function tests returning to baseline, and even improving in some cases. In the pilot study, mean FEV1 is within 4% of baseline and mean DLCO is within 6% of baseline by one year after HDIT. This is maintained at 3 years, with the median FVC improving by 7% and the median DLCO being within 3% of baseline.

The way forward

A certain subset of patients with SSc have a high mortality but have few therapeutic options. In that group the use of HDIT with TBI has yielded very significant skin improvements and major improvements in their quality of life.

Given the above data on TBI plus CYC, which document increased immunosuppression compared to CYC alone, it is possible that combination CYC plus TBI will be more efficacious than CYC alone. On the other hand, there is the possibility that TBI may be more toxic than CYC without TBI, although data to date do not seem to indicate such increased toxicity (i.e., with the revised TBI regimen). The only way to test this possibility is with a controlled trial.

For this reason, North America and the European Union are collaborating closely in a set of 2 protocols, whose inclusion and exclusion criteria and followup are almost identical, while control regimens are identical. The North American study includes G-CSF for mobilization and conditioning with ATG, 120 mg/kg CYC, plus TBI. The US National Institutes of Health, the Food and Drug Administration, and an independent data and safety monitoring board have reviewed and approved it for appropriate design and to ensure safety concerns are addressed. The protocol under the auspices of the European Union uses G-CSF plus CYC for mobilization, plus conditioning with ATG and 200 mg/kg CYC, but not TBI. In this way, a rational and reasonable test of an intensive immunosuppressive regimen that includes TBI can be conducted for efficacy and safety.

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